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(54) **Potentiation of serotonin response**

Potenzierung von Serotonin-Wirkstoffresponz

Potentialisation de la sérotonine

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(56) References cited:
EP-A- 0 687 472 **EP-A- 0 714 663**

- ACTA PHARMACOLOGICA ET TOXICOLOGICA, vol. 55, 1984, pages 363-372, XP000607318
ARNT, HYTTTEL, LARSEN: "THE CITALOPRAM / 5-HTP INDUCED HEAD SHAKE SYNDROME IS CORRELATED TO 5-HT₂ RECEPTOR AFFINITY AND ALSO INFLUENCED BY OTHER TRANSMITTERS"
- EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 260, 1994, pages 251-255, XP000605645
HJORTH, AUERBACH: "FURTHER EVIDENCE FOR THE IMPORTANCE OF 5-HT_{1A} AUTORECEPTORS IN THE ACTION OF SSRI"

- ARCHIVES OF GENERAL PSYCHIATRY, vol. 51, no. 3, 1994, pages 248-251, XP000605678
ARTIGAS ET AL: "PINDOLOL INDUCES A RAPID IMPROVEMENT OF DEPRESSED PATIENTS TREATED WITH SEROTONIN REUPTAKE INHIBITORS"
- BRITISH JOURNAL OF PHARMACOLOGY, vol. 115, 1995, pages 1064-1070, XP000604130
GARTSIDE ET AL: "interaction between a selective 5-HT_{1A} receptor antagonist and a SSRI in vivo: Effects ... extracellular 5-HT"
- JOURNAL OF NEUROCHEMISTRY, vol. 60, no. 2, 1993, pages 776-779, XP000604419 HJORTH: "serotonin 5-HT_{1A} autoreceptor blockade potentiates the ability of ... citalopram to increase nerve terminal output of 5-HT ..."
- EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 264, 1994, pages 241-247, XP000607292
SANCHEZ, HYTTTEL: "ISOLATION-INDUCED AGGRESSION IN MICE: EFFECTS OF 5-HT UPTAKE INHIBITORS AND INVOLVEMENT OF POSTSYNAPTIC 5-HT_{1A} RECEPTORS243"
- RESEARCH COMMUNICATIONS IN CHEMICAL PATHOLOGY AND PHARMACOLOGY, vol. 28, no. 2, 1980, pages 343-349, XP000607300 LAHTI, BARSUHN: "THE EFFECT OF ANTIDEPRESSANTS ON L-5HTP-INDUCED CHANGES IN RAT PLASMA CORTICOSTEROIDS"
- PHARMACOLOGY BIOCHEMISTRY & BEHAVIOR, vol. 55, no. 1, 1996, pages 1-10, XP000607290 DARMANI, REEVES: "THE MECHANISM BY WHICH THE SELECTIVE 5HT_{1A} RECEPTOR ANTAGONIST (S)-UH-301 PRODUCES HEAD-TWITCHES IN MICE"

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Description

[0001] The present invention belongs to the fields of pharmacology, medicine and medicinal chemistry, and provides methods and compositions for increasing the availability of serotonin, norepinephrine and dopamine in the brain of patients.

[0002] Over the past twenty years or more, the science of pharmacology has been particularly interested in the physiology of the neurons containing monoamines in the human brain. Discovery has followed discovery in the field and it has now been demonstrated that serotonin, norepinephrine and dopamine interact with a great number of receptors in the brain and control or affect processes which regulate many bodily organs and functions. Serotonin, particularly, has been found to be the key to a large number of processes which reveal themselves in both physiological and psychological functions.

[0003] Perhaps the most dramatic discovery in medicinal chemistry in the recent past is fluoxetine, a serotonin reuptake inhibitor, which is extremely effective in the treatment of depression. As a reuptake inhibitor, it increases the availability of serotonin in the synapse by reducing the uptake of serotonin by the serotonin uptake carrier. Excessive uptake results in depression, as well as other pathologies of the central nervous system. Not only is fluoxetine spectacularly effective in depression, it is also effective in treating numerous other conditions.

[0004] While the primary activity of fluoxetine and related drugs is the inhibition of the reuptake of serotonin, the cascade of monoamine processes in the brain connects serotonin with both norepinephrine and dopamine. Thus, the increase of availability of serotonin results in increased availability of norepinephrine and dopamine as well.

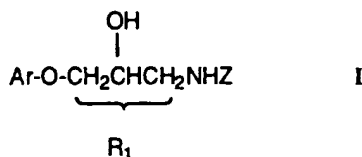
[0005] It has been recently discovered that blockade at the serotonin 1A receptor, particularly with antagonist activity, is also related to the availability of serotonin, and hence of norepinephrine and dopamine, in the brain. E.g., Artigas et al., *Arch. Gen. Psychiatry* 51, 248-251 (1994); Hjorth, *J. Neurochem.* 60, 776-779 (1993). Certain 5-HT_{1A} antagonists are now in clinical trials as potentiators of serotonin reuptake inhibitors. The full benefit of providing compounds which effectively block the 5-HT_{1A} receptor has not yet been explored, nor has the best method of exploiting the relationship between the 5-HT_{1A} receptor and other serotonin processes been provided to the medical arts.

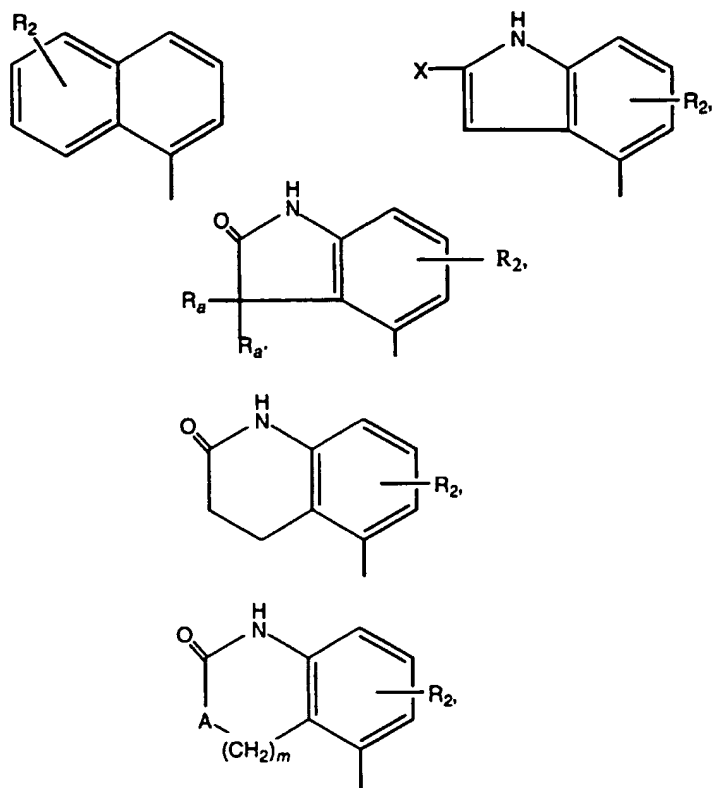
[0006] The present invention provides means for increasing the availability of serotonin, norepinephrine and dopamine, even compared to the usual increased availability caused by treatment with fluoxetine and related drugs which have followed it.

[0007] In one embodiment the invention provides the combined use of a serotonin 1A receptor antagonist and a compound selected from L-tryptophan, 5-hydroxy-L-tryptophan or a pharmaceutically acceptable salt thereof for preparing a medicament for potentiating the action of a serotonin reuptake inhibitor in increasing the availability of serotonin, norepinephrine and dopamine in the brain.

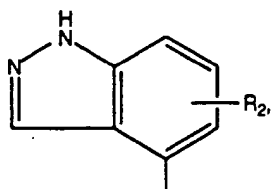
[0008] In another embodiment the invention provides a pharmaceutical composition which comprises a first component which is a serotonin reuptake inhibitor, a second component which is a serotonin 1A receptor antagonist, and a third component which is L-tryptophan or 5-hydroxy-L-tryptophan or a pharmaceutically acceptable salt thereof.

[0009] In a further embodiment the invention provides a pharmaceutical composition for potentiating the action of a first component chosen from the group consisting of fluoxetine, venlafaxine, citalopram, fluvoxamine, paroxetine, sertraline, milnacipran, and duloxetine in increasing the availability of serotonin, norepinephrine and dopamine in the brain, said composition comprising said first component in combination with a second component chosen from the group consisting of alprenolol, WAY 100135, WAY 100635, spiperone, pindolol, (S)-UH-301, penbutolol, propranolol, tertatolol, and a compound of the formula

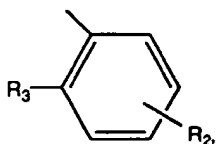




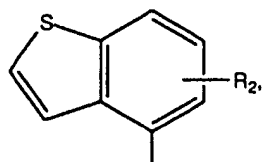
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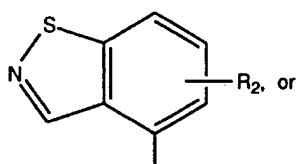
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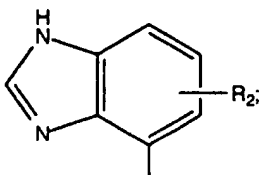
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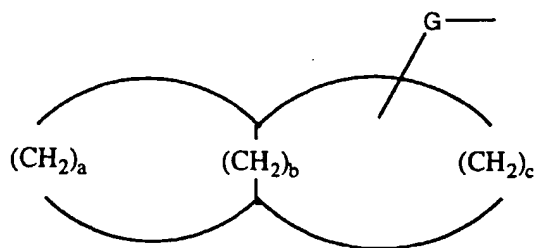


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R_1 is an optional methyl group substituted on one of the three connecting carbon atoms;
 R_2 is hydrogen, C_1 - C_4 alkyl, trifluoromethyl, hydroxy, $(C_1$ - C_4 alkyl)-O-, $(C_1$ - C_4 alkyl) -S(O) $_p$ -, or halo;
 R_3 is C_3 - C_8 cycloalkyl or a bicycloalkyl group of the formula

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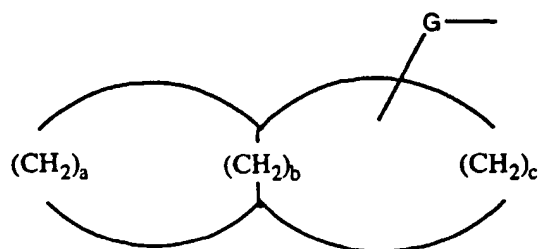


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where a and c are independently 1-5, b is 0-5, and (a+c) is greater than 2;
Z is a straight or branched C_4 - C_{10} alkane, alkene, or alkyne group; $(C_4$ - C_8 cycloalkyl) optionally substituted with
 C_1 - C_4 alkyl or phenyl; a bicycloalkyl group of the formula

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wherein a and c are independently 1-5, b is 0-5, and (a+c) is greater than 2; optionally phenyl substituted C₂-C₁₀ alkyl where the phenyl group can be optionally substituted with R₂ as previously defined; or (C₁-C₄ alkylidene)-T-(C₁-C₄ alkyl), where T is -O-, -S-, -SO-, or -SO₂-; where each G is independently a bond or C₁-C₄ alkylidene; X is -H-, -COY-, -CN-, or C₁-C₄ alkyl; Y is -OH-, -O-(C₁-C₄ alkyl), or -NH₂; R_a and R_{a'} are independently hydrogen or C₁-C₃ alkyl, or when taken together with the carbon atom to which they are attached form a C₃-C₈ cycloalkyl ring; p is 0, 1, or 2; A is -O-, -S-, -NH-, or -NCH₃-; and m is 0, 1, 2, or 3;

and with a third component chosen from the group consisting of L-tryptophan and 5-hydroxy-L-tryptophan; or a pharmaceutically acceptable salt thereof.

[0010] The pharmaceutical compositions of the invention can be used in methods of treating a pathological condition which is created by or is dependent upon decreased availability of serotonin, dopamine or norepinephrine, which comprise administering to a patient in need of such treatment an adjunctive therapy comprising a first component, a second component and a third component compound.

[0011] Still further, a preferred manner of carrying out the above method of adjunctive therapy wherein the second component is administered in a manner which provides a substantially constant blood level of the second component, which level is sufficient to provide a substantially constant degree of potentiation of the action of the first component. Compositions adapted for carrying out the preferred manner of are also provided.

[0012] In a more general sense, the embodiment making use of the first, second and third component compounds is also a method of potentiating the action of the first component, where the first component is a serotonin reuptake inhibitor in the general sense; the second component compound is an antagonist at the 5-HT_{1A} receptor in a general sense; and the third component is L-tryptophan or 5-hydroxy-L-tryptophan or a salt thereof.

[0013] In this document, all temperatures are described in degrees Celsius, and all amounts, ratios of amounts and concentrations are described in weight units unless otherwise stated.

The Compounds

[0014] Fluoxetine, N-methyl-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine, is marketed in the hydrochloride salt form, and as the racemic mixture of its two enantiomers. U.S. Patent 4,314,081 is an early reference on the compound. Robertson et al., *J. Med. Chem.* **31**, 1412 (1988), taught the separation of the R and S enantiomers of fluoxetine and showed that their activity as serotonin uptake inhibitors is similar to each other. In this document, the word "fluoxetine" will be used to mean any acid addition salt or the free base, and to include either the racemic mixture or either of the R and S enantiomers.

[0015] Duloxetine, N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine, is usually administered as the hydrochloride salt and as the (+) enantiomer. It was first taught by U.S. Patent 4,956,388, which shows its high potency. The word "duloxetine" will be used here to refer to any acid addition salt or the free base of the molecule.

[0016] Venlafaxine is known in the literature, and its method of synthesis and its activity as an inhibitor of serotonin and norepinephrine uptake are taught by U.S. Patent 4,761,501. Venlafaxine is identified as compound A in that patent.

[0017] Milnacipran (N,N-diethyl-2-aminomethyl-1-phenylcyclopropanecarboxamide) is taught by U.S. Patent 4,478,836, which prepared milnacipran as its Example 4. The patent describes its compounds as antidepressants. Moret et al., *Neuropharmacology* **24**, 1211-19 (1985), describe its pharmacological activities as an inhibitor of serotonin and norepinephrine reuptake.

[0018] Citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, is disclosed in U.S. Patent 4,136,193 as a serotonin reuptake inhibitor. Its pharmacology was disclosed by Christensen et al., *Eur. J. Pharmacol.* **41**, 153 (1977), and reports of its clinical effectiveness in depression may be found in Dufour et al., *Int. Clin. Psychopharmacol.* **2**, 225 (1987), and Timmerman et al., *ibid.*, 239.

[0019] Fluvoxamine, 5-methoxy-1-[4-(trifluoromethyl)-phenyl]-1-pentanone O-(2-aminoethyl)oxime, is taught by U. S. Patent 4,085,225. Scientific articles about the drug have been published by Claassen et al., *Brit. J. Pharmacol.* **60**, 505 (1977); and De Wilde et al., *J. Affective Disord.* **4**, 249 (1982); and Benfield et al., *Drugs* **32**, 313 (1986).

[0020] Paroxetine, trans-(-)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine, may be found in U.S. Patents 3,912,743 and 4,007,196. Reports of the drug's activity are in Lassen, *Eur. J. Pharmacol.* **47**, 351 (1978); Hassan et al., *Brit. J. Clin. Pharmacol.* **19**, 705 (1985); Laursen et al., *Acta Psychiat. Scand.* **71**, 249 (1985); and Battegay et al., *Neuropsychobiology* **13**, 31 (1985).

[0021] Sertraline, (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine hydrochloride, is a serotonin reuptake inhibitor which is marketed as an antidepressant. It is disclosed by U.S. Patent 4,536,518.

[0022] Duloxetine and fluoxetine, as well as the other first components, are known to increase the availability of serotonin (5-HT), dopamine (DA) and norepinephrine (NE), and the second component drugs potentiate that valuable property through their activity as antagonists of the serotonin 1A receptor.

[0023] (S)-UH-301 ((S)-5-fluoro-8-hydroxy-2-dipropylaminotetralin) is well known to pharmacologists and pharmaceutical chemists. Hillver et al. taught its synthesis in *J. Med. Chem.* **33**, 1541-44 (1990) and Moreau et al., *Brain Res. Bull.* **29**, 901-04 (1992) provided considerable in vivo data about the compound.

[0024] Alprenolol (1-(1-methylethyl)amino-3-[2-(2-propenyl)-phenoxy]-2-propanol) was disclosed by Brandstrom et al., U.S. Patent 3,466,325, which shows its preparation as Example 5.

[0025] WAY 100135 (N-(t-butyl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]-2-phenylpropanamide) was disclosed by Abou-Gharbia et al., U.S. Patent 4,988,814, who taught that the compound has affinity for the 5-HT_{1A} receptor. Cliffe et al., *J. Med. Chem.* **36**, 1509-10 (1993) showed that the compound is a 5-HT_{1A} antagonist.

[0026] WAY 100635 (N-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-N-(2-pyridyl)cyclohexanecarboxamide) was put in the literature by Cliffe et al., European Patent Publication 0512755, published November 11, 1992. A number of papers about the compound and its activity as a 5-HT_{1A} antagonist were presented at the IUPHAR Satellite Meeting on Serotonin, July 30, 1994, Chicago, IL, and abstracts were published.

[0027] Spiperone (8-[4-(4-fluorophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one) is a well-known compound, taught in U.S. Patents 3,155,669 and 3,155,670. Its activity as a 5-HT_{1A} antagonist is shown by Middlemiss et al., *Neurosci. and Biobehav. Rev.* **16**, 75-82 (1992).

[0028] Tertatolol (8-(3-t-butylamino-2-hydroxypropyloxy)-thiochroman) was disclosed by Malen et al., U.S. Patent 3,960,891, which teaches it to be a blocker of cardiac beta-adrenergic receptors. Its other activities, including the presently used 5-HT_{1A} antagonist activity, have been discovered since the original patents appeared.

[0029] Propranolol (1-isopropylamino-3-(1-naphthalenyloxy)-2-propanol) was disclosed by Crowther et al., U.S. Patent 3,337,628 to be a beta-blocker like tertatolol. Again, its other properties are also well known to pharmacologists.

[0030] Penbutolol (1-(t-butylamino)-2-hydroxy-3-(2-cyclopentyl-phenoxy)propane) was taught by Ruschig et al., U.S. Patent 3,551,493, which describes it as a beta-blocker. Both the (-) and the (+) enantiomers of penbutolol are of interest; the (-) enantiomer is preferred for the present purpose but both enantiomers and the racemic mixture are included in the word "penbutolol" in this document.

[0031] Pindolol (4-(2-hydroxy-3-isopropylaminopropoxy)-indole) was disclosed by Troxler et al., U.S. Patent 3,471,515, which describes this compound as well as a beta-blocker. The compound is usually administered as the racemic mixture, but the two enantiomers have been isolated and the (-) enantiomer is preferred if a single isomer product is desired in a given application. Both enantiomers and the racemic mixture are included in the word "pindolol" in this document.

[0032] The compounds of formula I are taught by Beedle, et al., U.S. patent 5,013,761, the description of which is incorporated herein by reference. The synthesis and characteristics, including the 5-HT_{1A} antagonist activity, of the compounds is shown in that patent.

[0033] The particularly preferred compounds of formula I include, for example, the following individual compounds. It will be understood that the following compounds are typical of those of formula 1 but that the compounds include numerous other valuable species as shown by the previously mentioned U.S. patent. It will be further understood that, while individual salts, and in some cases, enantiomers, are mentioned below and are of particular interest, other salts, and enantiomers, diastereomers, and racemates, are likewise valuable and are included in formula I as agents for the present invention.

1-(4-indolyloxy)-3-cyclohexylamino-2-propanol, maleate salt;
 cis-1-(4-indolyloxy)-3-(4-phenylcyclohexyl-amino)-2-propanol, oxalate salt;
 1-(4-indolyloxy)-3-(2-phenylethylamino)-2-propanol, oxalate salt;

1-(4-indolyloxy)-3-cyclopentylamino-2-propanol, maleate salt;
 1-(4-indolyloxy)-3-(4-phenylbutylamino)-2-propanol, maleate salt;
 1-(4-indolyloxy)-3-cyclopentylamino-2-propanol, maleate salt;
 1-(4-indolyloxy)-3-cycloheptylamino-2-propanol;
 5 (S)-(-)-1-(4-indolyloxy)-3-cyclohexylamino-2-propanol, maleate salt;
 (+)-1-(4-indolyloxy)-3-cyclohexylamino-2-propanol, maleate salt;
 1-(4-indolyloxy)-3-(3-methylcyclohexylamino)-2-propanol;
 1-(4-indolyloxy)-3-(4-methylcyclohexylamino)-2-propanol;
 1-(4-indolyloxy)-3-(5-phenylpentylamino)-2-propanol, oxalate salt;
 10 1-(4-indolyloxy)-3-(6-phenylhexylamino)-2-propanol, oxalate salt;
 1-(4-indolyloxy)-3-(2,3-dimethylcyclohexylamino)-2-propanol, oxalate salt;
 (+)-1-(4-indolyloxy)-3-(3-pentylamino)-2-propanol;
 (R)-(+)-1-(4-indolyloxy)-3-cyclohexylamino-2-propanol, butanedioate salt;
 (R)-(-)-1-(4-indolyloxy)-3-cyclohexylamino-2-propanol, butanedioate salt;
 15 1-(2-trifluoromethyl-4-benzimidazolyl)-3-(4-phenylbutylamino)-2-propanol;
 (exo)-1-(4-indolyloxy)-3-(norbornylamino)-2-propanol;
 (endo)-1-(4-indolyloxy)-3-(norbornylamino)-2-propanol;
 1-(1-naphthalenyloxy)-3-cycloheptylamino-2-propanol, oxalate salt;
 1-(2-cyclopentylphenoxy)-3-cycloheptylamino-2-propanol, oxalate salt;
 20 1-(2-cyclohexylphenoxy)-3-cyclooctylamino-2-propanol, oxalate salt;
 1-(2-cycloheptylphenoxy)-3-(1,2,3-trimethyl-2-propylamino)-2-propanol, oxalate salt; and
 1-(2-cyclopropylphenoxy)-3-(1,1-dimethylbutylamino)-2-propanol, oxalate salt.

[0034] The group of the compounds of formula I wherein the group Ar is indolyl or substituted indolyl constitutes a
 25 further preferred class of 5-HT_{1A} antagonists; and the compounds of formula I wherein Z is (C₄-C₈ cycloalkyl) optionally
 substituted with C₁-C₄ alkyl or phenyl; or Z represents optionally phenyl substituted C₂-C₁₀ alkyl where the phenyl
 group can be optionally substituted with R₂; constitute further particularly preferred classes of compounds for use in
 the present invention.

[0035] The third component compounds are L-tryptophan and 5-hydroxy-L-tryptophan, which are amino acids known
 30 to every scientist who is involved in any life science.

[0036] All of the U.S. patents which have been mentioned above in connection with compounds used in the present
 invention are incorporated herein by reference.

[0037] While all combinations of first, second and third component compounds are useful and valuable, certain com-
 35 binations are particularly valued and are preferred, as follows:

fluoxetine/pindolol/5-hydroxy-L-tryptophan
 duloxetine/pindolol/5-hydroxy-L-tryptophan
 fluoxetine/penbutolol/5-hydroxy-L-tryptophan
 duloxetine/penbutolol/L-tryptophan
 40 fluoxetine/propranolol/5-hydroxy-L-tryptophan
 duloxetine/propranolol/L-tryptophan
 fluoxetine/tertatolol/L-tryptophan
 duloxetine/tertatolol/5-hydroxy-L-tryptophan
 fluoxetine/4-(2-hydroxy-3-cyclohexylaminopropoxy)-indole/L-tryptophan
 45 duloxetine/4-(2-hydroxy-3-cyclohexylaminopropoxy)-indole/5-hydroxy-L-tryptophan

[0038] In general, combinations and methods of treatment using fluoxetine or duloxetine as the first component are
 preferred.

[0039] It will be understood by the skilled reader that most or all of the compounds used in the present invention are
 50 capable of forming salts, and that the salt forms of pharmaceuticals are commonly used, often because they are more
 readily crystallized and purified than are the free bases. In all cases, the use of the pharmaceuticals described above
 as salts is contemplated in the description herein, and often is preferred, and the pharmaceutically acceptable salts of
 all of the compounds are included in the names of them.

[0040] Many of the compounds used in this invention are amines, and accordingly react with any of a number of
 55 inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Since some of the free amines of
 the compounds of this invention are typically oils at room temperature, it is preferable to convert the free amines to
 their pharmaceutically acceptable acid addition salts for ease of handling and administration, since the latter are rou-
 tinely solid at room temperature. Acids commonly employed to form such salts are inorganic acids such as hydrochloric

acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids, such as *p*-toluene-sulfonic acid, methanesulfonic acid, oxalic acid, *p*-bromo-phenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid and the like. Examples of such pharmaceutically acceptable salts thus are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, mono-hydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propionate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methyl-benzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, *b*-hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable salts are those formed with hydrochloric acid, oxalic acid or fumaric acid.

[0041] Some of the compounds used in this invention are acidic in nature, or have both acidic and basic groups. Accordingly, salts can be formed with basic substances, such as the alkali and alkali metal hydroxides, carbonates and bicarbonates, alkylamines, ammonia, quaternary ammonium compounds and the like. Such salts include, for example, sodium, calcium, ammonium, diethylamine, diethanolamine, trimethylamine, diethyldibutylammonium, tetraphenylammonium, diphenyldioctylammonium and related salts.

[0042] In the general expressions of the present invention, the first component is a compound which acts as a serotonin reuptake inhibitor. The measurement of a compound's activity in that utility is now a standard pharmacological assay. Wong, et al., *Neuropsychopharmacology* 8, 337-344 (1993). Many compounds, including those discussed at length above, have such activity, and no doubt many more will be identified in the future. In the practice of the present invention, it is intended to include reuptake inhibitors which show 50% effective concentrations of about 1000 nM or less, in the protocol described in the article just mentioned.

[0043] Similarly, when the invention is regarded in its broadest sense, the second component compound is a compound which functions as an antagonist at the 5-HT_{1A} receptor. The 1A receptor has been successfully cloned, and cell lines which produce the receptor are available. Thus, it is not a difficult task for a pharmacologist to screen compounds to determine their activity as 5-HT_{1A} antagonists. It will be understood, of course, that active compounds often combine more than one activity, and that compounds frequently are both antagonists and agonists at the same receptor, in various degrees. In the context of the present invention, the term "5-HT_{1A} antagonist" is used to mean a substance which is substantially fully antagonistic, that is to say, in the range of about 70% antagonistic or more, and only 30% agonistic or less, at the 5-HT_{1A} receptor. Wong, et al., *Neuropsychopharmacology* 5, 43-47 (1991).

Administration

[0044] The dosages of the drugs used in the present invention must, in the final analysis, be set by the physician in charge of the case, using knowledge of the drugs, the properties of the drugs in combination as determined in clinical trials, and the characteristics of the patient, including diseases other than that for which the physician is treating the patient. General outlines of the dosages, and some preferred dosages, can and will be provided here. Dosage guidelines for some of the drugs will first be given separately; in order to create a guideline for any desired combination, one would choose the guidelines for each of the component drugs.

Fluoxetine: from about 1 to about 80 mg, once/day; preferred, from about 10 to about 40 mg once/day; preferred for bulimia and obsessive-compulsive disease, from about 20 to about 80 mg once/day;

Duloxetine: from about 1 to about 30 mg once/day; preferred, from about 5 to about 20 mg once/day;

Venlafaxine: from about 10 to about 150 mg once-thrice/day; preferred, from about 25 to about 125 mg thrice/day;

Milnacipran: from about 10 to about 100 mg once-twice/day; preferred, from about 25 to about 50 mg twice/day;

Citalopram: from about 5 to about 50 mg once/day; preferred, from about 10 to about 30 mg once/day;

Fluvoxamine: from about 20 to about 500 mg once/day; preferred, from about 50 to about 300 mg once/day;

Paroxetine: from about 20 to about 50 mg once/day; preferred, from about 20 to about 30 mg once/day.

Sertraline: from about 20 to about 500 mg once/day; preferred, from about 50 to about 200 mg once/day;

Pindolol: from about 1 to about 60 mg once-thrice/day; once-thrice/day; preferred, from about 5 to about 60 mg also preferred, from about 1 to about 10 mg twice/day;

Penbutolol: from about 2 to about 80 mg once/day; preferred, from about 10 to about 80 mg once/day; also preferred, from about 2 to about 20 mg once/day;

Propranolol: from about 10 to about 240 mg once-twice/day; preferred, from about 10 to about 120 mg twice/day; also preferred, from about 40 to about 240 mg once-twice/day;

4-(2-Hydroxy-3-cyclohexylaminopropoxy)indole: from about 1 to about 50 mg once-twice/day; preferred, from about 1 to about 10 mg twice/day;

L-Tryptophan and 5-hydroxy-L-tryptophan: from about 1 to about 1000 mg/day.

[0045] In more general terms, one would create a combination of the present invention by choosing a dosage of first component compound according to the above guideline, and choosing dosages of the second compound in the general range of from about 1 to about 240 mg/dose. More preferred dosages, depending on the compound, would be from about 1 to about 100 mg/dose, and even more preferred dosages would be likely to be found in the range of from about 1 to about 50 mg/dose, ideally from about 1 to about 25 mg/dose. Similarly, one would choose a dose of the third component in the above range, more preferably in a range from about 10 to about 1000 mg/day, but always in a range chosen with regard to the effects of the first and second components.

[0046] The adjunctive therapy of the present invention is carried out by administering a first component together with one each of the second and third component compounds in any manner which provides effective levels of the compounds in the body at the same time. All of the compounds concerned are orally available and are normally administered orally, and so oral administration of the adjunctive combination is preferred. They may be administered together, in a single dosage form, or may be administered separately.

[0047] However, oral administration is not the only route or even the only preferred route. For example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine. One of the drugs may be administered by one route, such as oral, and the others may be administered by the transdermal, percutaneous, intravenous, intramuscular, intranasal or intrarectal route, in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs and the convenience of the patient and the caregiver.

[0048] It is particularly preferred, however, for the adjunctive combination to be administered as a single pharmaceutical composition, and so pharmaceutical compositions incorporating all the compounds are important embodiments of the present invention. Such compositions may take any physical form which is pharmaceutically acceptable, but orally usable pharmaceutical compositions are particularly preferred. Such adjunctive pharmaceutical compositions contain an effective amount of each of the compounds, which effective amount is related to the daily dose of the compounds to be administered. Each adjunctive dosage unit may contain the daily doses of all compounds, or may contain a fraction of the daily doses, such as one-third of the doses. Alternatively, each dosage unit may contain the entire dose of one of the compounds, and a fraction of the dose of the other compounds. In such case, the patient would daily take one of the combination dosage units, and one or more units containing only the other compounds. The amounts of each drug to be contained in each dosage unit depends on the identity of the drugs chosen for the therapy, and other factors such as the indication for which the adjunctive therapy is being given.

[0049] The second component compounds, taken as a class, have short lives in the body and, accordingly, provide only short periods of activity following each dose. For example, pindolol is routinely administered twice/day in the prior art, and it has been administered even more often. In the context of the present invention, it is therefore preferred to administer the second component compounds in a manner which supplies a substantially constant blood level of the second component in the body of the patient, at a sufficiently high level to provide a substantially constant degree of potentiation of the action of the first component.

[0050] It is not intended, of course, that the present invention or any method of human treatment can provide a truly constant blood level and degree of potentiation. Biological processes always vary and prevent precisely constant results. The term "substantially constant" is used herein to refer to administration resulting in blood levels and degrees of potentiation which are sufficiently constant as to provide continuous improved efficacy over a treatment day, compared to the efficacy of the first component compound alone. Another way to consider substantially constant potentiation is by comparing the availability of serotonin, norepinephrine and dopamine in the brain of the patient. By "substantially constant" in such terms is meant a condition where the peak and the valley of availability differ by no more than about a factor of 2 over the course of a treatment day. Another way to consider "substantially constant" is a condition where the peak and valley differ by no more than about a factor of 1.5; or they differ by no more than a range of from about 1.5 to about 3.

[0051] Such administration of the second component may be provided by means known to pharmaceutical scientists. For example, the total daily dosage of a second component may be formulated in a manner which provides a substantially constant flow of compound to the patient. To consider only pindolol, at least the following references teach sustained release formulations: German Patent 3632201, capsules; Swiss Patent 634990, tablets; German Patent 3237945, buccal tape; German Patent 2732335, tablets; U.S. Patent 5260066, cryogels; European Patent Publication 361894, liposomes; Japanese Patent 84-66710, transdermal patches. Pharmaceutical scientists are acquainted in modern practice with the manners of adjusting a sustained release formulation to provide the desired rate of administration of a given compound and such formulations can be prepared by the skill of the pharmaceutical art of the compounds used as second components here.

[0052] Such formulations of a second component compound may be combined in a single dosage form with the other chosen compounds. For example, a small tablet or pellets of the second component, formulated to provide constant availability of the compound, may be combined, for example in a capsule, with the first and third component compounds. Alternatively, a transdermal patch may be prepared which has a relatively rapidly releasing area, and a relatively slowly

releasing area of second component. Still further, a suspension may be prepared in which the first and third components are present as solution or particles of pure compound, and the particles of the second component are coated to provide sustained release in the body. In such manners, the availability of the second component may be adjusted to provide the desired substantially constant blood levels and, hence, substantially constant potentiation of the first component. Compositions so adapted for providing substantially constant potentiation of the first component are preferred compositions of the present invention.

[0053] The inert ingredients and manner of formulation of the adjunctive pharmaceutical compositions are conventional, except for the presence of the combination of the present invention. The usual methods of formulation used in pharmaceutical science may be used here. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, intranasal sprays or powders, troches, suppositories, transdermal patches and suspensions. In general, compositions contain from about 0.5% to about 50% of the compounds in total, depending on the desired doses and the type of composition to be used. The amount of the compounds, however, is best defined as the effective amount, that is, the amount of each compound which provides the desired dose to the patient in need of such treatment. The activity of the adjunctive combinations do not depend on the nature of the composition, so the compositions are chosen and formulated solely for convenience and economy. Any of the combinations may be formulated in any desired form of composition. Some discussion of different compositions will be provided, followed by some typical formulations.

[0054] Capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

[0055] Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidone and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

[0056] A lubricant is necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

[0057] Tablet disintegrators are substances which swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algin and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used, as well as sodium lauryl sulfate.

[0058] Enteric formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are created by coating a solid dosage form with a film of a polymer which is insoluble in acid environments, and soluble in basic environments. Exemplary films are cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate. It is preferred to formulate duloxetine and duloxetine-containing combinations as enteric compositions, and even more preferred to formulate them as enteric pellets.

[0059] A preferred duloxetine enteric formulation is a pellet formulation comprising a) a core consisting of duloxetine and a pharmaceutically acceptable excipient; b) an optional separating layer; c) an enteric layer comprising hydroxypropylmethylcellulose acetate succinate (HPMCAS) and a pharmaceutically acceptable excipient; d) an optional finishing layer. The following example demonstrates the preparation of a preferred such formulation.

Example

[0060]

10 mg Duloxetine base/capsule	
Bill of Materials	
Beads Sucrose - starch nonpareils, 20-25 mesh	60.28 mg
Duloxetine layer	

(continued)

10 mg Duloxetine base/capsule		
Bill of Materials		
	Duloxetine	11.21
	Hydroxypropylmethylcellulose	3.74
	Separating layer	
	Hydroxypropylmethylcellulose	2.51
	Sucrose	5.00
	Talc, 500 mesh	10.03
	Enteric layer	
	HPMCAS, LF grade, Shin-Etsu Chemical Co., Tokyo, Japan	25.05
	Triethyl citrate	5.00
	Talc, 500 mesh	7.52
	Finishing layer	
	Hydroxypropylmethylcellulose	8.44
	Titanium dioxide	2.81
	Talc	<u>Trace</u>
		141.60 mg

[0061] The duloxetine layer was built up by suspending duloxetine in a 4% w/w solution of the hydroxypropylmethylcellulose in water, and milling the suspension with a CoBall Mill (Fryma Mashinen AG, Rheinfelden, Switzerland) model MS-12. A fluid bed dryer with a Wurster column was used to make this product, at a batch size of 1.0 kg. The separating layer was added from a 4% w/w solution of the hydroxypropylmethylcellulose in water, in which the sucrose was also dissolved.

[0062] In order to prepare the enteric coating suspension, purified water was cooled to 10°C and the polysorbate, triethyl citrate and silicone emulsion were added and dispersed or dissolved. Then the HPMCAS and talc were added and agitated until homogeneity was obtained, and the HPMCAS was fully neutralized by addition of ammonium hydroxide until solution of the polymer was complete. To this suspension, a carboxymethylcellulose aqueous solution, 0.5% w/w, was added and blended thoroughly. The enteric suspension was maintained at 20°C during the coating process. The enteric suspension was then added to the partially completed pellets in the Wurster column at a spray rate of about 15 ml/min, holding the temperature of the inlet air at about 50°C. The product was dried in the Wurster at 50°C when the enteric suspension had been fully added, and then dried on trays for 3 hours in a dry house at 60°C. A finishing layer was then applied which consisted of a 4.5% w/w/ hydroxypropylmethylcellulose solution containing titanium dioxide and propylene glycol as plasticizer. The pellets were completely dried in the fluid bed dryer and then were then filled in size 3 gelatin capsules.

[0063] Tablets are often coated with sugar as a flavor and sealant, or with film-forming protecting agents to modify the dissolution properties of the tablet. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established practice. Instantly dissolving tablet-like formulations are also now frequently used to assure that the patient consumes the dosage form, and to avoid the difficulty in swallowing solid objects that bothers some patients.

[0064] When it is desired to administer the combination as a suppository, the usual bases may be used. Cocoa butter is a traditional suppository base, which may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use, also.

[0065] Transdermal patches have become popular recently. Typically they comprise a resinous composition in which the drugs will dissolve, or partially dissolve, which is held in contact with the skin by a film which protects the composition. Many patents have appeared in the field recently. Other, more complicated patch compositions are also in use, particularly those having a membrane pierced with innumerable pores through which the drugs are pumped by osmotic action.

[0066] The following typical formulae are provided for the interest and information of the pharmaceutical scientist.

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Formulation 1

[0067] Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Fluoxetine, racemic, hydrochloride	20 mg
Pindolol	30
5-Hydroxy-L-tryptophan	50
Starch, dried	150
Magnesium stearate	10
Total	260 mg

Formulation 2

[0068] A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
Fluoxetine, racemic, hydrochloride	10
(-)-Penbutolol	40
5-Hydroxy-L-tryptophan	125
Cellulose, microcrystalline	275
Silicon dioxide, fumed	10
Stearic acid	5
Total	465 mg

The components are blended and compressed to form tablets each weighing 465 mg.

Formulation 3

[0069] An aerosol solution is prepared containing the following components:

	Weight
(+) -Duloxetine, hydrochloride	10
Pindolol	10
L-Tryptophan	10
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	60.00
Total	115.75

[0070] The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4

[0071] Tablets, each containing 80 mg of active ingredient, are made as follows:

(+) -Duloxetine, hydrochloride	20 mg
(-)-Penbutolol	60 mg
L-Tryptophan	30
Starch	30 mg
Microcrystalline cellulose	20 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg

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(continued)

Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	170 mg

[0072] The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinyl- pyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. Sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 170 mg.

Formulation 5

[0073] Capsules, each containing 130 mg of active ingredient, are made as follows:

Fluoxetine, racemic, hydrochloride	30 mg
Propanolol	100 mg
5-Hydroxy-L-tryptophan	40 mg
Starch	39 mg
Microcrystalline cellulose	39 mg
Magnesium stearate	2 mg
Total	250 mg

[0074] The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 250 mg quantities.

Formulation 6

[0075] Suppositories, each containing 45 mg of active ingredient, are made as follows:

(+) -Duloxetine, hydrochloride	5 mg
Propranolol	40 mg
L-Tryptophan	200 mg
Saturated fatty acid glycerides	2,000 mg
Total	2,245 mg

[0076] The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 7

[0077] Suspensions, each containing 70 mg of active ingredient per 5 ml dose, are made as follows:

Fluoxetine, racemic, hydrochloride	10 mg
Propranolol	60 mg
5-Hydroxy-L-tryptophan	100 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.

(continued)

Color	q.v.
Purified water to total	5 ml

[0078] The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

[0079] An intravenous formulation may be prepared as follows:

(+)-Duloxetine, hydrochloride	10 mg
Propanolol	20 mg
L-Tryptophan	300 mg
Isotonic saline	1,000 ml

Benefit of the Invention

[0080] The present invention potentiates and augments the increased availability of serotonin, norepinephrine and dopamine caused by the first component compound, conferring a marked and unexpected benefit on the patient.

[0081] As stated above, the increase in availability of serotonin is particularly important and is a preferred aspect of the invention. Further, the invention provides a more rapid onset of action than is usually provided by treatment with serotonin-affecting drugs.

[0082] Preferred pathological conditions to be treated by the present method of adjunctive therapy include depression, obsessive-compulsive disease and obesity. Another preferred condition more specific to combinations including preferably duloxetine but also venlafaxine and milnacipran is urinary incontinence.

[0083] Depression in its many variations has recently become much more visible to the general public than it has previously been. It is now recognized as an extremely damaging disorder, and one that afflicts a surprisingly large fraction of the population. Suicide is the most extreme symptom of depression, but millions of people, not quite so drastically afflicted, live in misery and partial or complete uselessness, and afflict their families as well by their affliction. The introduction of fluoxetine was a breakthrough in the treatment of depression, and depressives are now much more likely to be diagnosed and treated than they were only a decade ago.

[0084] Depression is often associated with other diseases and conditions, or caused by such other conditions. For example, it is associated with Parkinson's disease; with HIV; with Alzheimer's disease; and with abuse of anabolic steroids. Depression may also be associated with abuse of any substance, or may be associated with behavioral problems resulting from or occurring in combination with head injuries, mental retardation or stroke. Depression in all its variations is a preferred target of treatment with the present adjunctive therapy method and compositions.

[0085] Obsessive-compulsive disease appears in a great variety of degrees and symptoms, generally linked by the patient's uncontrollable urge to perform needless, ritualistic acts. Acts of acquiring, ordering, cleansing and the like, beyond any rational need or rationale, are the outward characteristic of the disease. A badly afflicted patient may be unable to do anything but carry out the rituals required by the disease. Fluoxetine is approved in the United States and other countries for the treatment of obsessive-compulsive disease and has been found to be effective.

[0086] Obesity is a frequent condition in the population of developed countries. It has been found that fluoxetine will enable an obese patient to lose weight, with the resulting benefit to the patient's circulation and heart condition, as well as general well being and energy.

[0087] Urinary incontinence is classified generally as stress or urge incontinence, depending on whether its root cause is the inability of the sphincter muscles to keep control, or the overactivity of the bladder muscles. Duloxetine controls both types of incontinence, or both types at once, and so is important to the many people who suffer from this embarrassing and disabling disorder.

[0088] The present invention is useful for treating many other diseases, disorders and conditions as well, as set out below. In many cases, the diseases to be mentioned here are classified in the International Classification of Diseases, 9th Edition (ICD), or in the Diagnostic and Statistical Manual of Mental Disorders, 3rd Version Revised, published by the American Psychiatric Association (DSM). In such cases, the ICD or DSM code numbers are supplied below for the convenience of the reader.

depression, ICD 296.2 & 296.3, DSM 296, 294.80, 293.81, 293.82, 293.83, 310.10, 318.00, 317.00 migraine
 pain, particularly neuropathic pain
 bulimia, ICD 307.51, DSM 307.51
 premenstrual syndrome or late luteal phase
 5 syndrome, DSM 307.90
 alcoholism, ICD 305.0, DSM 305.00 & 303.90
 tobacco abuse, ICD 305.1, DSM 305.10 & 292.00
 panic disorder, ICD 300.01, DSM 300.01 & 300.21
 anxiety, ICD 300.02, DSM 300.00
 10 post-traumatic syndrome, DSM 309.89
 memory loss, DSM 294.00
 dementia of aging, ICD 290
 social phobia, ICD 300.23, DSM 300.23
 attention deficit hyperactivity disorder, ICD 314.0
 15 disruptive behavior disorders, ICD 312
 impulse control disorders, ICD 312, DSM 312.39 & 312.34
 borderline personality disorder, ICD 301.83, DSM 301.83
 chronic fatigue syndrome
 premature ejaculation, DSM 302.75
 20 erectile difficulty, DSM 302.72
 anorexia nervosa, ICD 307.1, DSM 307.10
 disorders of sleep, ICD 307.4
 autism
 mutism
 25 trichotillomania

Experimental Results

[0089] Representative combinations of the present invention have been tested in conscious experimental animals
 30 and the surprising results of the testing demonstrate the benefit of the invention. The tests were carried out as follows.

Microdialysis assays of monoamines

[0090] Sprague-Dawley rats (Harlan or Charles River) weighing 270-300 grams were surgically implanted with micro-
 35 dialysis probes under chloral hydrate/pentobarbital anesthesia (170 and 36 mg/kg i.p. in 30% propylene glycol, 14%
 ethanol) (Perry and Fuller, Effect of fluoxetine on serotonin and dopamine concentration in rat hypothalamus after
 administration of fluoxetine plus L-5-hydroxytryptophan, *Life Sci.*, 50, 1683-90 (1992)). A David Kopf stereotaxic in-
 strument was used to implant the probe unilaterally in the hypothalamus at coordinates rostral -1.5 mm, lateral -1.3
 40 mm, and ventral -9.0 mm (Paxinos and Watson, 1986). After a 48 hour recovery period, rats were placed in a large
 plastic bowl with a mounted liquid swivel system (CMA/120 system for freely moving animals, Bioanalytical Systems,
 West Lafayette, IN). Filtered artificial cerebrospinal fluid (CSF) (150 mM NaCl, 3.0 mM KCl, 1.7 mM CaCl₂, and 0.9
 mM MgCl₂) was perfused through the probe at a rate of 1.0 ml/min. The output dialysate line was fitted to a tenport
 HPLC valve with a 20 µl loop. At the end of each 30 minute sampling period, dialysate collected in the loop was injected
 on an analytical column (Spherisorb 3 µ ODS2, 2X150 mm, Keystone Scientific).

45 [0091] The method used to measure monoamines was as described by Perry and Fuller (1992). Briefly, dialysate
 collected in the 20 µl loop was assayed for 5-HT, NE and DA. The 20 µl injection went onto the column with a mobile
 phase which resolved NE, DA, and 5-HT: 75 mM potassium acetate, 0.5 mM ethylenediaminetetraacetic acid, 1.4 mM
 sodium octanesulfonic acid and 8% methanol, pH 4.9. The mobile phase for the amine column was delivered with a
 flow programmable pump at an initial flow rate of 0.2 ml/min increasing to 0.3 ml/min at 5 min then decreasing back
 50 to 0.2 ml/min at 26 min with a total run time of 30 min. Flow programming was used to elute the 5-HT within a 25 min
 time period. The electrochemical detector (EG&G, Model 400) for the amine column was set at a potential of 400 mV
 and a sensitivity of 0.2 nA/V. The data was collected and analyzed with a Hewlett-Packard HP1000 chromatography
 system which measured peak heights and calculated sample concentrations. Basal levels were measured for at least
 90 minutes prior to drug administration. The drugs were prepared in filtered deionized water and administered (volume
 55 0.25-0.3 ml) at the doses stated in the results below.

Evaluation and Statistical Analyses

[0092] Extracellular levels of the amines in microdialysates were calculated by comparing peak heights with those of 50 pmole standards. The mean value of the four samples immediately preceding drug administration served as the basal level for each experiment and data was converted to percent of basal. Paired t-tests were used to compare the mean of the basal values from the time point immediately preceding drug administration to those of each time point thereafter.

[0093] The data has been rounded to make the trends more visible.

Test 1

[0094] In this test, the combination therapy comprised fluoxetine as the hydrochloride of the racemate, (-)-pindolol, and L-tryptophan. The rats were prepared as described above, and L-tryptophan administered intraperitoneally at 100 mg/kg, 150 minutes after the start of the experiment. Pindolol was administered subcutaneously at 5 mg/kg, at 270 minutes after the start of the experiment. A mixture of fluoxetine (10 mg/kg) and pindolol (10 mg/kg) was administered intraperitoneally at 390 minutes after the start of the experiment. L-Tryptophan was administered intraperitoneally at 100 mg/kg, at 420 minutes after the beginning of the experiment. Each data point reported here represents a single animal.

Time (minutes)	5-HT	Time (minutes)	5-HT	Time (minutes)	5-HT
30	120.9	240	76.3	450	390.1
60	122.7	270	73.9	480	530.5
90	79.4	300	56.8	510	631.3
120	104.4	330	42.1	540	747.9
150	72.6	360	45.2	570	780.2
180	88.5	390	44.6		
210	83.6	420	216.1		

[0095] Administration of a mixture of fluoxetine and pindolol at 390 minutes followed by the administration of tryptophan 30 minutes later resulted in a remarkable increase in serotonin concentration to nearly 800% of basal levels. The administration of fluoxetine and pindolol alone has been reported to increase serotonin levels to 400% of basal levels (Dreshfield, *et al.*, *Neurochemical Research*, 21(5), 557-562 (1996)).

Test 2

[0096] In this test, the combination therapy comprised fluoxetine as the hydrochloride of the racemate, pindolol as the racemate, and L-tryptophan. Pindolol was continuously infused subcutaneously at a rate of 50 mg/kg/hr beginning at 120 minutes after the beginning of the experiment. Fluoxetine was administered intraperitoneally at 10 mg/kg, 240 minutes after the start of the experiment. L-Tryptophan was administered intraperitoneally at 100 mg/kg, 420 minutes after the start of the experiment. The results are shown below as percent of baseline of the three monoamines, at various times after the start of the experiment. Each data point reported here represents a single animal.

Time (min.)	5-HT (%)	NE (%)	DA (%)
30	112.0	54.7	89.7
60	103.0	102.4	104.2
90	91.0	107.5	102.3
120	94.0	135.4	103.4
150	67.7	221.5	87.2
180	64.7	273.5	73.2
210	27.4	232.5	70.3
240	18.8	261.9	68.5
270	98.1	841.3	78.2
300	197.4	579.6	73.8
330	250.4	548.5	67.6

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(continued)

Time (min.)	5-HT (%)	NE (%)	DA (%)
360	270.7	548.0	66.5
390	246.2	658.0	58.3
420	273.7	609.2	63.4
450	371.8	914.1	72.9
480	475.2	1397.7	99.4
510	518.4	1542.3	105.7
540	540.2	1596.8	106.3

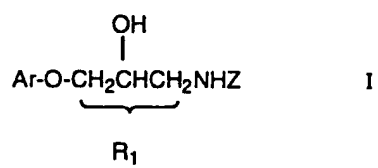
Test 3

[0097] In this test, the combination therapy comprised fluoxetine as the hydrochloride of the racemate and L-tryptophan for purposes of comparison. Fluoxetine was administered intraperitoneally at 10 mg/kg, 100 minutes after the start of the experiment. L-Tryptophan was administered intraperitoneally at 100 mg/kg, 340 minutes after the start of the experiment. The results are shown below as percent of baseline of serotonin at various times after the start of the experiment. Each data point reported here represents the average value for from 3 to 5 test animals as indicated by the variable "N".

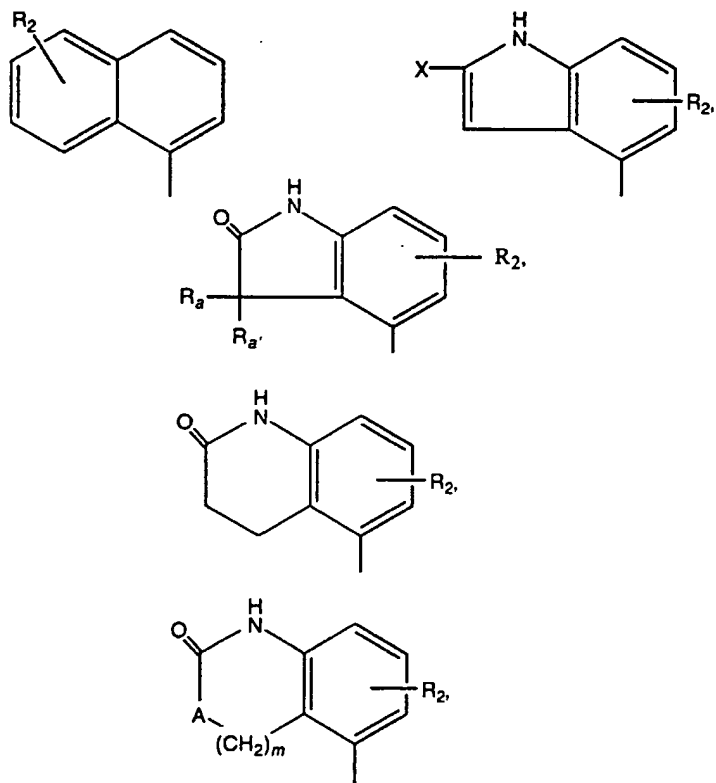
TIME (min.)	% 5-HT	Standard Error	N
20	114.8	28.4	4
40	100.0	12.8	5
60	86.8	10.6	5
80	105.8	5.6	5
100	123.9	37.2	5
120	115.3	20.8	5
140	129.0	7.4	5
160	163.6	23.8	5
180	101.6	37.9	5
200	141.5	8.2	5
220	158.2	10.2	5
240	155.7	23.9	5
260	118.5	14.2	5
280	167.3	39.2	5
300	126.6	16.8	5
320	187.7	47.6	5
340	190.1	25.5	5
360	163.7	32.2	5
380	198.5	110.0	3
400	207.5	24.6	3

Claims

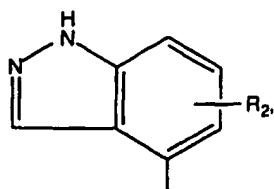
1. The combined use of a serotonin 1A receptor antagonist and a compound selected from L-tryptophan, 5-hydroxy-L-tryptophan or a pharmaceutically acceptable salt thereof for preparing a medicament for potentiating the action of a serotonin reuptake inhibitor in increasing the availability of serotonin, norepinephrine and dopamine in the brain.
2. The use of claim 1 in which the serotonin reuptake inhibitor is chosen from the group consisting of fluoxetine, venlafaxine, citalopram, fluvoxamine, paroxetine, sertraline, milnacipran and duloxetine, and the serotonin 1A receptor antagonist is chosen from the group consisting of alprenolol, WAY 100135, WAY 100635, spiperone, pindolol, (S)-UH-301, penbutolol, propranolol, tertatolol, and a compound of the formula



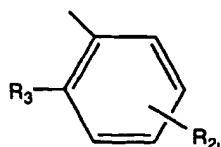
wherein Ar is



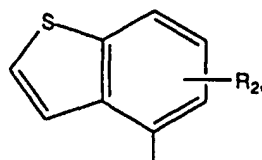
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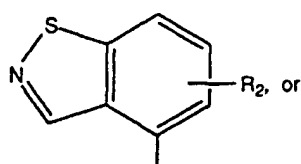
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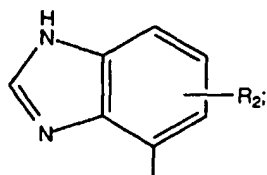
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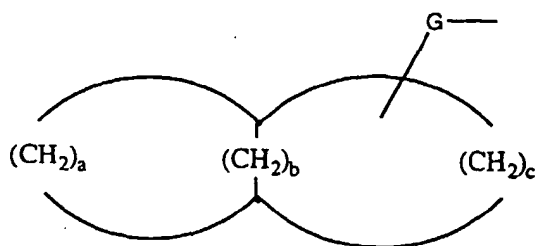


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R_1 is an optional methyl group substituted on one of the three connecting carbon atoms;
 R_2 is hydrogen, C_1 - C_4 alkyl, trifluoromethyl, hydroxy, $(C_1$ - C_4 alkyl)-O-, $(C_1$ - C_4 alkyl)-S(O)_p, or halo;
 R_3 is C_3 - C_8 cycloalkyl or a bicycloalkyl group of the formula

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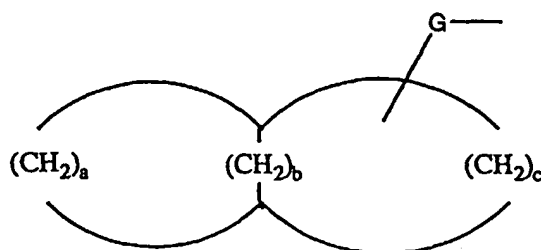


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where a and c are independently 1-5, b is 0-5, and (a+c) is greater than 2;
Z is a straight or branched C_4 - C_{10} alkane, alkene, or alkyne group; $(C_4$ - C_8 cycloalkyl) optionally substituted with C_1 - C_4 alkyl or phenyl; a bicycloalkyl group of the formula

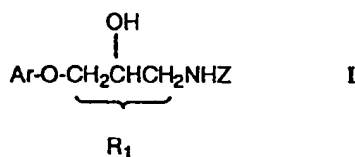
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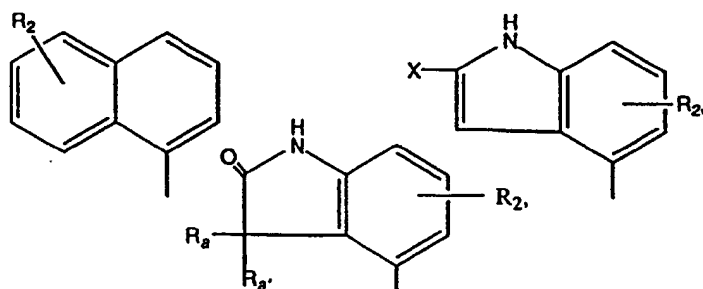


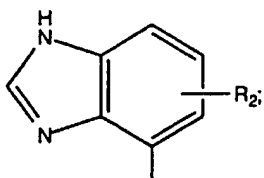
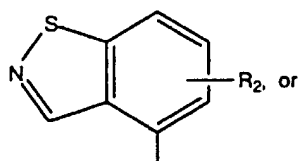
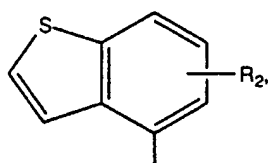
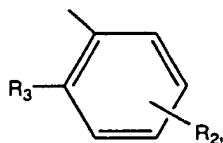
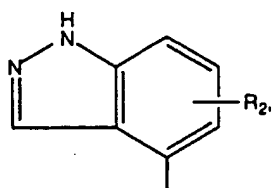
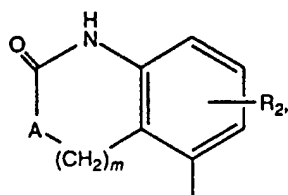
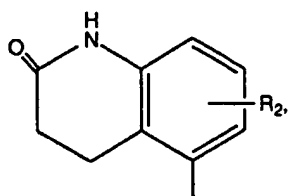
wherein a and c are independently 1-5, b is 0-5, and (a+c) is greater than 2; optionally phenyl substituted C₂-C₁₀ alkyl where the phenyl group can be optionally substituted with R₂ as previously defined; or (C₁-C₄ alkylidene)-T-(C₁-C₄ alkyl), where T is -O-, -S-, -SO-, or -SO₂-; where each G is independently a bond or C₁-C₄ alkylidene; X is -H, -COY, -CN, or C₁-C₄ alkyl; Y is -OH, -O-(C₁-C₄ alkyl), or -NH₂; R_a and R_{a'} are independently hydrogen or C₁-C₃ alkyl, or when taken together with the carbon atom to which they are attached form a C₃-C₈ cycloalkyl ring; p is 0, 1, or 2; A is -O-, -S-, -NH-, or -NCH₃-; and m is 0, 1, 2, or 3.

3. The use of claim 1 wherein the serotonin reuptake inhibitor is fluoxetine or duloxetine.
4. The use of claim 1 for increasing the availability of serotonin.
5. The use of claim 1 wherein the compounds are adapted for oral administration.
6. The use of claim 1 wherein the increased availability of serotonin, norepinephrine and dopamine provides treatment of a pathological condition.
7. The use of claim 6 wherein the pathological condition is depression.
8. A pharmaceutical composition which comprises a first component which is a serotonin reuptake inhibitor, a second component which is a serotonin 1A receptor antagonist, and a third component which is L-tryptophan or 5-hydroxy-L-tryptophan or a pharmaceutically acceptable salt thereof.
9. A composition of claim 8 which comprises a first component chosen from the group consisting of fluoxetine, venlafaxine, citalopram, fluvoxamine, paroxetine, sertraline, milnacipran and duloxetine in combination with a second component chosen from the group consisting of alprenolol, WAY 100135, WAY 100635, spiperone, pindolol, (S)-UH-301, penbutolol, propranolol, tertatolol, and a compound of the formula

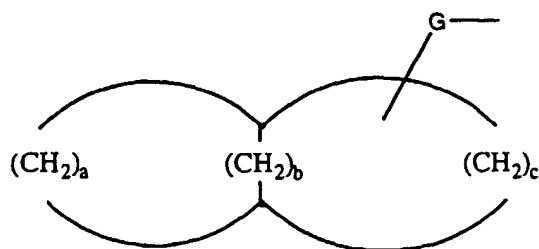


wherein Ar is

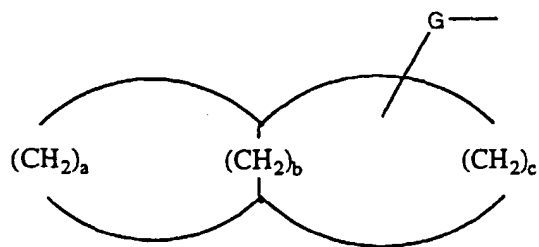




R_1 is an optional methyl group substituted on one of the three connecting carbon atoms;
 R_2 is hydrogen, C_1 - C_4 alkyl, trifluoromethyl, hydroxy, $(C_1$ - C_4 alkyl)-O-, $(C_1$ - C_4 alkyl)-S(O) $_p$ -, or halo;
 R_3 is C_3 - C_8 cycloalkyl or a bicycloalkyl group of the formula



15 where a and c are independently 1-5, b is 0-5, and (a+c) is greater than 2;
Z is a straight or branched C₄-C₁₀ alkane, alkene, or alkyne group; (C₄-C₈ cycloalkyl) optionally substituted
with C₁-C₄ alkyl or phenyl; a bicycloalkyl group of the formula



30 wherein a and c are independently 1-5, b is 0-5, and (a+c) is greater than 2; optionally phenyl substituted
C₂-C₁₀ alkyl where the phenyl group can be optionally substituted with R₂ as previously defined; or (C₁-C₄
alkylidene)-T-(C₁-C₄ alkyl), where T is -O-, -S-, -SO-, or -SO₂-; where
each G is independently a bond or C₁-C₄ alkylidene;
X is -H, -COY, -CN, or C₁-C₄ alkyl;
Y is -OH, -O-(C₁-C₄ alkyl), or -NH₂;
R_a and R_{a'} are independently hydrogen or C₁-C₃ alkyl, or when taken together with the carbon atom to which
they are attached form a C₃-C₈ cycloalkyl ring;
p is 0, 1, or 2;
A is -O-, -S-, -NH-, or -NCH₃-; and
m is 0, 1, 2, or 3;

40 and with a third component chosen from the group consisting of L-tryptophan and 5-hydroxy-L-tryptophan;
or a pharmaceutically acceptable salt thereof.

10. A composition of claim 8 which is adapted for oral administration.

11. A composition of claim 8 wherein the first component compound is fluoxetine or duloxetine.

12. A composition of claim 10 wherein the first component compound is fluoxetine or duloxetine.

13. A composition of claim 8 wherein the second component compound is pindolol, penbutolol, propranolol, tertatolol
or 4-(2-hydroxy-3-cyclohexylaminopropoxy) indole.

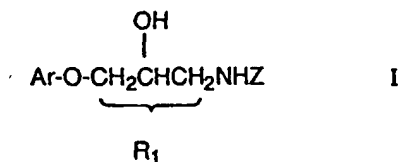
14. A composition of claim 12 wherein the second component compound is pindolol, penbutolol, propranolol, tertatolol
or 4-(2-hydroxy-3-cyclohexylaminopropoxy)indole.

55 Patentansprüche

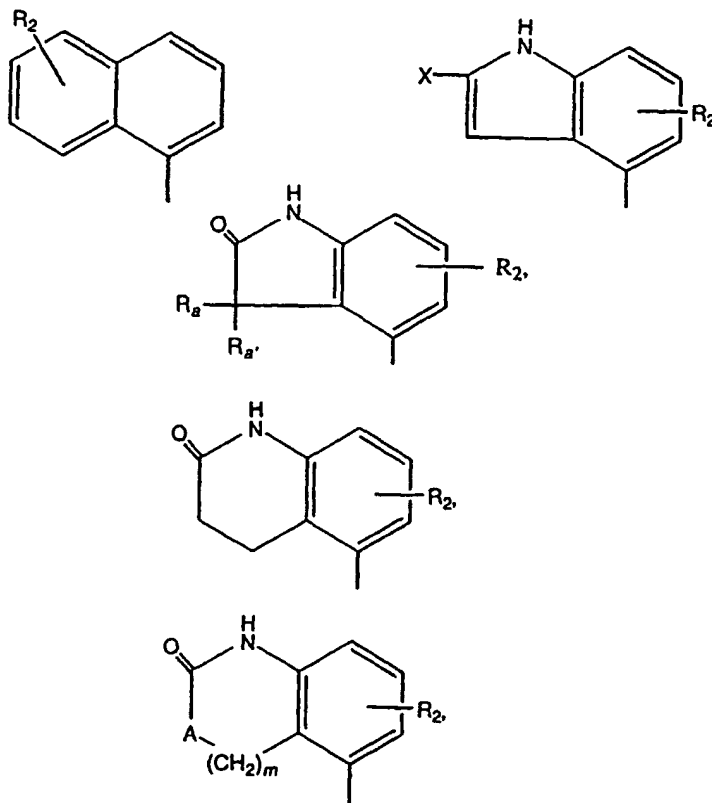
1. Kombinierte Verwendung eines Serotonin-1A-rezeptorantagonisten und einer Verbindung ausgewählt aus L-Tryptophan, 5-Hydroxy-L-tryptophan oder einem pharmazeutisch annehmbaren Salz hiervon zur Herstellung eines

Arzneimittels zur Verstärkung der Wirkung eines Serotoninwiederaufnahmehemmers bei der Erhöhung der Verfügbarkeit von Serotonin, Norepinephrin und Dopamin im Gehirn.

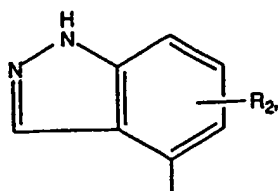
2. Verwendung nach Anspruch 1, worin der Serotoninwiederaufnahmehemmer ausgewählt ist aus der Gruppe, die besteht aus Fluoxetin, Venlafaxin, Citalopram, Fluvoxamin, Paroxetin, Sertralin, Milnacipran und Duloxetin, und der Serotonin-1A-rezeptorantagonist aus der Gruppe ausgewählt ist, die besteht aus Alprenolol, WAY 100135, WAY 100635, Spiperon, Pindolol, (S)-UH-301, Penbutolol, Propranolol, Tertatolol und einer Verbindung der Formel



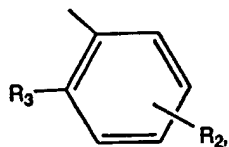
worin Ar steht für



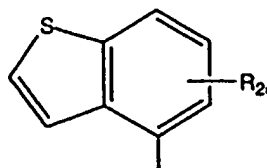
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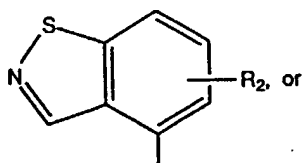
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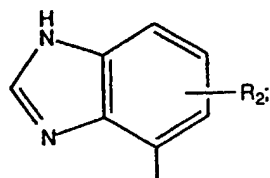
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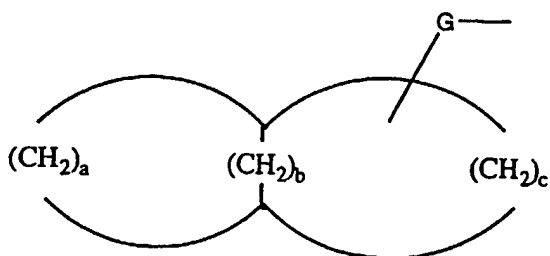
R_1 für eine optionale Methylgruppe steht, die an einem der drei verbindenden Kohlenstoffatome als Substituent vorkommt,

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R_2 für Wasserstoff, C_1 - C_4 Alkyl, Trifluormethyl, Hydroxy, $(C_1$ - C_4 Alkyl)-O-, $(C_1$ - C_4 Alkyl)-S(O)_p- oder Halogen steht,

R_3 für C_3 - C_8 Cycoalkyl oder eine Bicycloalkylgruppe der folgenden Formel steht

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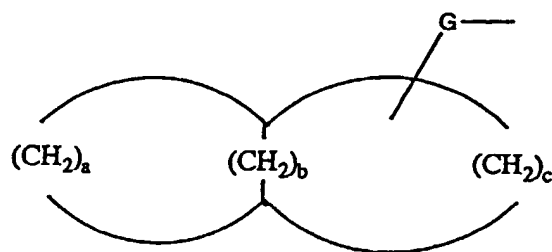


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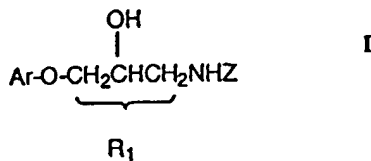
worin a und c unabhängig für 1-5 stehen, b für 0-5 steht und (a+c) größer als 2 ist, Z steht für eine gerade oder verzweigte C_4 - C_{10} -Alkan-, -Alken- oder -Alkingruppe, (C_4 - C_8 Cycloalkyl), das wahlweise substituiert ist mit C_1 - C_4 Alkyl oder Phenyl, eine Bicycloalkylgruppe der Formel

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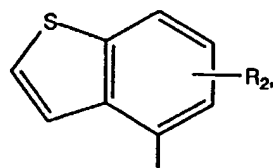
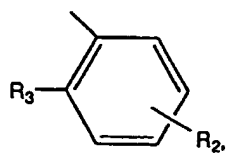
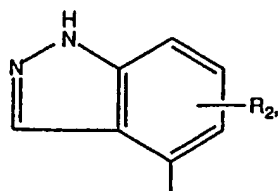
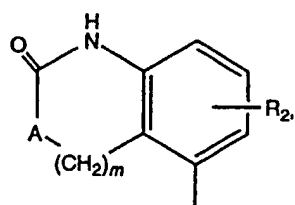
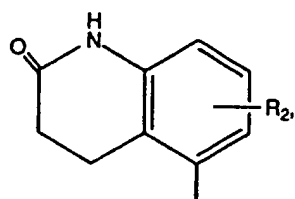
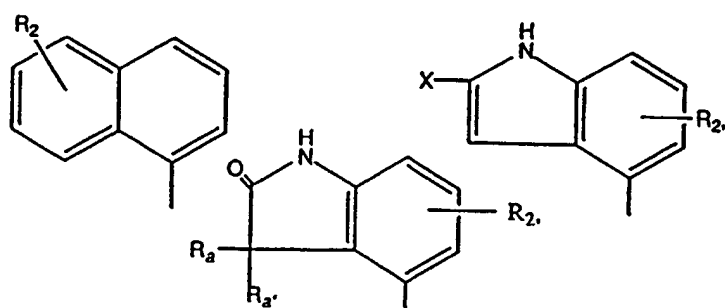


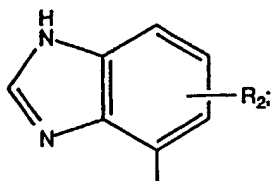
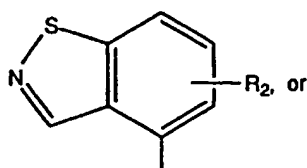
worin a und c unabhängig für 1-5 stehen, b für 0-5 steht und (a+c) größer als 2 ist, für wahlweise mit Phenyl substituiertes C₂-C₁₀ Alkyl, worin die Phenylgruppe wahlweise mit R₂ substituiert sein kann, wie dies vorher definiert wurde, oder für (C₁-C₄ Alkyliden-T-(C₁-C₄ Alkyl), worin T für -O-, -S-, -SO- oder -SO₂- steht, worin jedes G unabhängig für eine Bindung oder C₁-C₄ Alkyliden steht, X für -H, -COY, -CN, oder C₁-C₄ Alkyl steht, Y für -OH, -O-(C₁-C₄ Alkyl) oder -NH₂ steht, R_a und R_a, unabhängig für Wasserstoff oder C₁-C₃ Alkyl stehen, oder wenn sie mit dem Kohlenstoffatom, an das sie gebunden sind, zusammengekommen werden, einen C₃-C₈ Cycloalkylring bilden, p für 0, 1 oder 2 steht, A für -O-, -S-, -NH- oder -NCH₃- steht und m für 0, 1, 2 oder 3 steht.

3. Verwendung nach Anspruch 1, worin der Serotoninwiederaufnahmehemmer Fluoxetin oder Duloxetin ist.
4. Verwendung nach Anspruch 1 zur Erhöhung der Verfügbarkeit von Serotonin.
5. Verwendung nach Anspruch 1, worin die Verbindungen zur oralen Verabreichung angepaßt sind.
6. Verwendung nach Anspruch 1, worin die erhöhte Verfügbarkeit von Serotonin, Norepinephrin und Dopamin eine Behandlung eines pathologischen Zustands bereitstellt.
7. Verwendung nach Anspruch 6, worin der pathologische Zustand Depression ist.
8. Pharmazeutische Zusammensetzung, die enthält eine erste Komponente, die ein Serotoninwiederaufnahmehemmer ist, eine zweite Komponente, die ein Serotonin-1A-rezeptorantagonist ist, und eine dritte Komponente, die L-Tryptophan oder 5-Hydroxy-L-tryptophan oder ein pharmazeutisch annehmbares Salz hiervon ist.
9. Zusammensetzung nach Anspruch 8, die enthält eine erste Komponente, ausgewählt aus der Gruppe, die besteht aus Fluoxetin, Venlafaxin, Citalopram, Fluvoxamin, Paroxetin, Sertralin, Milnacipran und Duloxetin in Kombination mit einer zweiten Komponente, ausgewählt aus der Gruppe, die besteht aus Alprenolol, WAY 100135, WAY 100635, Spiperon, Pindolol, (S)-UH-301, Penbutolol, Propranolol, Tertatolol und einer Verbindung der Formel



worin Ar steht für

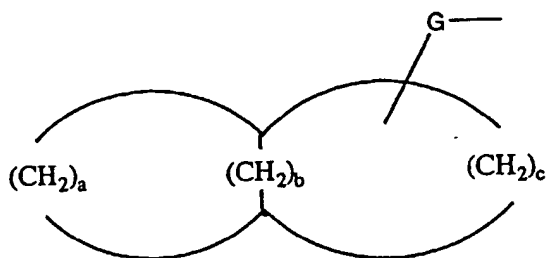




R_1 für eine optionale Methylgruppe steht, die an einem der drei verbindenden Kohlenstoffatome als Substituent vorkommt,

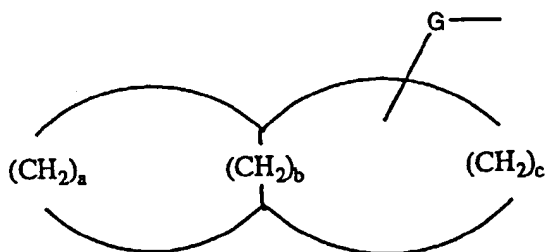
R_2 für Wasserstoff, C_1 - C_4 Alkyl, Trifluormethyl, Hydroxy, $(C_1$ - C_4 Alkyl)-O-, $(C_1$ - C_4 Alkyl)-S(O)_p- oder Halogen steht,

R_3 für C_3 - C_8 Cycloalkyl, eine Bicycloalkylgruppe der folgenden Formel steht



worin a und c unabhängig für 1-5 stehen, b für 0-5 steht und (a+c) größer als 2 ist,

Z steht für eine gerade oder verzweigte C_4 - C_{10} -Alkan-, -Alken- oder -Alkingruppe, (C_4 - C_8 Cycloalkyl), das wahlweise substituiert ist mit C_1 - C_4 Alkyl oder Phenyl, eine Bicycloalkylgruppe der folgenden Formel



worin a und c unabhängig für 1-5 stehen, b für 0-5 steht und (a+c) größer als 2 ist, für wahlweise mit Phenyl substituiertes C_2 - C_{10} Alkyl, worin die Phenylgruppe wahlweise mit R_2 substituiert sein kann, wie dies vorher definiert wurde, oder für $(C_1$ - C_4 Alkyliden)-T- $(C_1$ - C_4 Alkyl), worin T für -O-, -S-, -SO- oder -SO₂- steht, worin jedes G unabhängig für eine Bindung oder C_1 - C_4 Alkyliden steht,

X für -H-, -COY-, -CN-, oder C_1 - C_4 Alkyl steht,

Y für -OH-, -O- $(C_1$ - C_4 Alkyl) oder -NH₂ steht,

R_a und R_a' unabhängig für Wasserstoff oder C_1 - C_3 Alkyl stehen, oder wenn sie mit dem Kohlenstoffatom, an das sie gebunden sind, zusammengekommen werden, einen C_3 - C_8 Cycloalkylring bilden,

p für 0, 1 oder 2 steht,

A für -O-, -S-, -NH- oder -NCH₃- steht und
m für 0, 1, 2 oder 3 steht,

und eine dritte Komponente ausgewählt aus der Gruppe, die besteht aus L-Tryptophan und 5-Hydroxy-L-tryptophan, oder ein pharmazeutisch annehmbares Salz hiervon.

10. Zusammensetzung nach Anspruch 8, die zur oralen Verabreichung angepaßt ist.

11. Zusammensetzung nach Anspruch 8, worin die Verbindung der ersten Komponente Fluoxetin oder Duloxetin ist.

12. Zusammensetzung nach Anspruch 10, worin die Verbindung der ersten Komponente Fluoxetin oder Duloxetin ist.

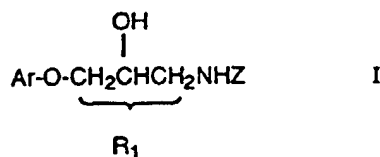
13. Zusammensetzung nach Anspruch 8, worin die Verbindung der zweiten Komponente Pindolol, Penbutolol; Propranolol, Tertatolol oder 4-(2-Hydroxy-3-cyclohexylaminopropoxy)indol ist.

14. Zusammensetzung nach Anspruch 12, worin die Verbindung der zweiten Komponente Pindolol, Penbutolol, Propranolol, Tertatolol oder 4-(2-Hydroxy-3-cyclohexylaminopropoxy)indol ist.

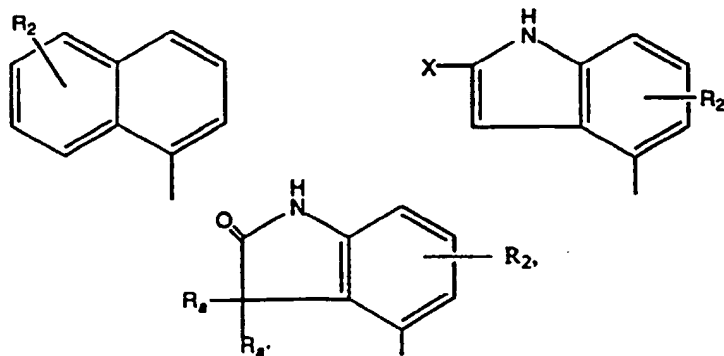
Revendications

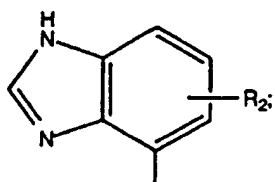
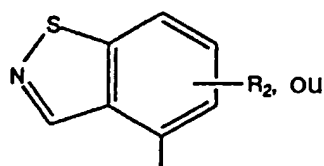
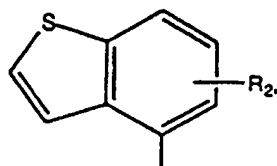
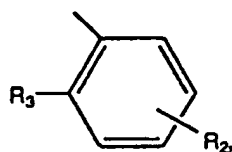
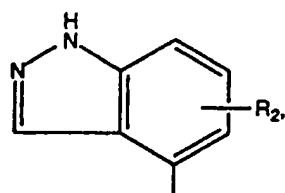
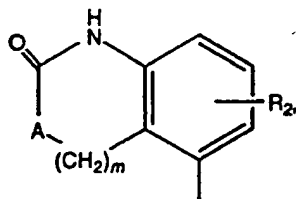
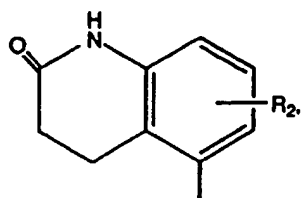
1. Utilisation combinée d'un antagoniste de récepteur 1A de la sérotonine et d'un composé choisi parmi le L-tryptophane, le 5-hydroxy-L-tryptophane ou un sel pharmaceutiquement acceptable de ceux-ci pour la préparation d'un médicament pour potentialiser l'action d'un inhibiteur de la réabsorption de la sérotonine dans l'accroissement de la disponibilité de la sérotonine, de la norépinéphrine et de la dopamine dans le cerveau.

2. Utilisation selon la revendication 1, dans laquelle l'inhibiteur de la réabsorption de la sérotonine est choisi dans le groupe constitué de la fluoxétine, de la venlafaxine, du citalopram, de la fluvoxamine, de la paroxétine, de la sertraline, du milnacipran et de la duloxétine et l'antagoniste du récepteur 1A de la sérotonine est choisi dans le groupe constitué de l'alprénolol, du WAY 100135, du WAY 100635, de la spipérone, du pindolol, du (S)-UH-301, du penbutolol, du propranolol, du tertatolol et un composé répondant à la formule

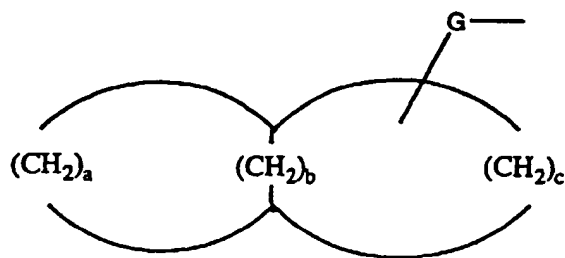


dans laquelle Ar représente



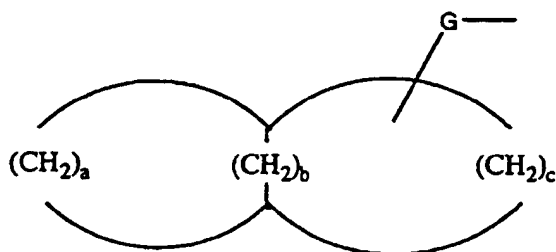


R_1 représente un groupe méthyle facultatif substitué sur un des trois atomes de carbone de connexion ;
 R_2 représente un atome d'hydrogène, un groupe alkyle en C_1-C_4 , un groupe trifluorométhyle, un groupe hydroxyle, un groupe (alkyle en C_1-C_4)-O-, un groupe (alkyle en C_1-C_4)-S(O) $_p$ -, ou un atome d'halogène ;
 R_3 représente un groupe cycloalkyle en C_3-C_8 ou un groupe bicycloalkyle répondant à la formule



où a et c valent, indépendamment l'un de l'autre, 1 - 5, b vaut 0 - 5, et (a + c) est supérieur à 2 ;
 Z représente un groupe alcane, alcène ou alcyne en C₄-C₁₀ linéaire ou ramifié ; un groupe (cycloalkyle en C₄-C₈) facultativement substitué par un groupe alkyle en C₁-C₄ ou par un groupe phényle ; un groupe bicycloalkyle répondant à la formule

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dans laquelle a et c valent, indépendamment l'un de l'autre, 1 - 5, b vaut 0 - 5, et (a + c) est supérieur à 2 ; un groupe alkyle en C₂-C₁₀ facultativement substitué par un groupe phényle, où le groupe phényle peut être facultativement substitué par R₂ tel qu'il a été défini précédemment ; ou un groupe -(alkylidène en C₁-C₄)-T- (alkyle en C₁-C₄), où T représente un groupe -O-, un groupe -S-, un groupe -SO-, ou un groupe -SO₂- ;

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où

chaque G représente, indépendamment l'un de l'autre, une liaison ou un groupe alkylidène en C₁-C₄ ;

X représente un groupe -H, un groupe -COY, un groupe -CN, ou un groupe alkyle en C₁-C₄ ;

Y représente un groupe -OH, un groupe -O-(alkyle en C₁-C₄) ou un groupe -NH₂ ;

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R_a et R_a représentent, indépendamment l'un de l'autre, un atome d'hydrogène ou un groupe alkyle en C₁-C₃, ou lorsqu'ils sont pris ensemble avec l'atome de carbone auquel ils sont attachés, ils forment un noyau cycloalkyle en C₃-C₈ ;

p vaut 0, 1 ou 2 ;

A représente un groupe -O-, un groupe -S-, un groupe -NH- ou un groupe -NCH₃- ; et

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m vaut 0, 1, 2 ou 3.

3. Utilisation selon la revendication 1, dans laquelle l'inhibiteur de la réabsorption de la sérotonine est la fluoxétine ou la duloxétine.

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4. Utilisation selon la revendication 1 pour accroître la disponibilité de la sérotonine.

5. Utilisation selon la revendication 1, dans laquelle les composés sont adaptés à l'administration orale.

6. Utilisation selon la revendication 1, dans laquelle la disponibilité accrue de la sérotonine, de la norépinéphrine et de la dopamine permet le traitement d'une condition pathologique.

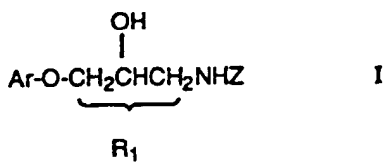
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7. Utilisation selon la revendication 6, dans laquelle la condition pathologique est la dépression.

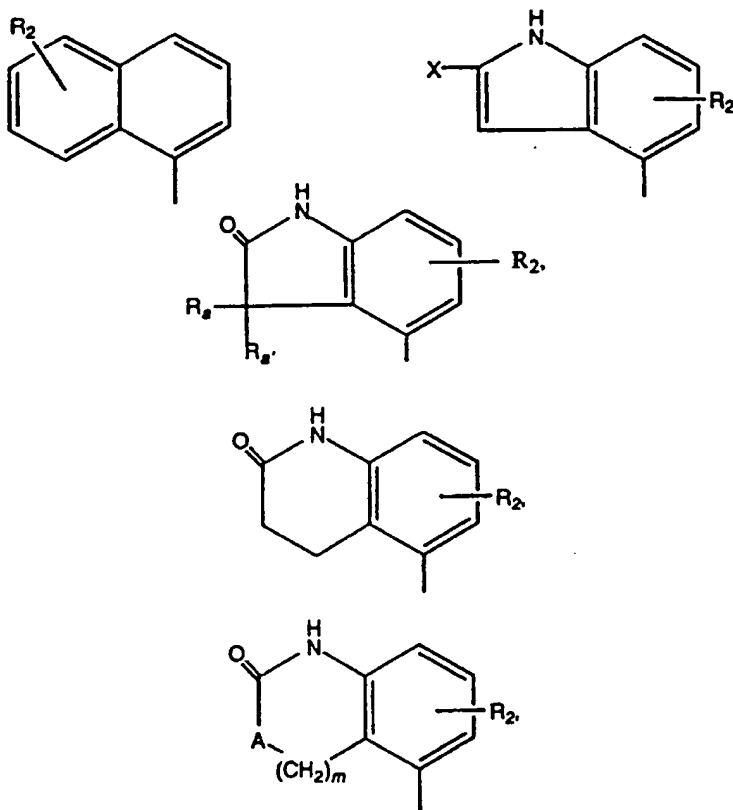
8. Composition pharmaceutique qui comprend un premier composant qui est un inhibiteur de la réabsorption de la sérotonine, un deuxième composant qui est un antagoniste du récepteur 1A de la sérotonine et un troisième composant qui est le L-tryptophane ou le 5-hydroxy-L-tryptophane ou un sel pharmaceutiquement acceptable de ceux-ci.

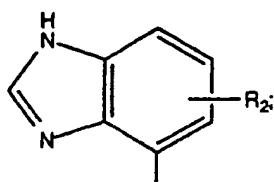
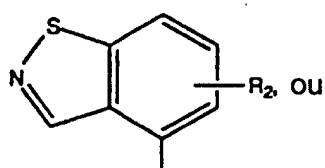
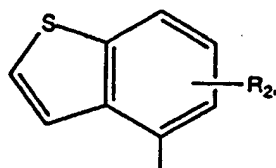
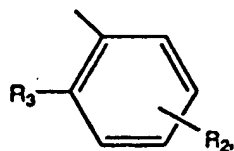
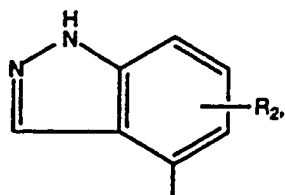
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9. Composition selon la revendication 8, qui comprend un premier composant choisi dans le groupe constitué de la fluoxétine, de la venlafaxine, du citalopram, de la fluvoxamine, de la paroxétine, de la sertraline, du milnacipran et de la duloxétine en combinaison avec un deuxième composant choisi dans le groupe constitué de l'alprénolol, du WAY 100135, du WAY 100635, de la spipéronne, du pindolol, du (S)-UH-301, du penbutolol, du propranolol, du tertatolol et un composé répondant à la formule

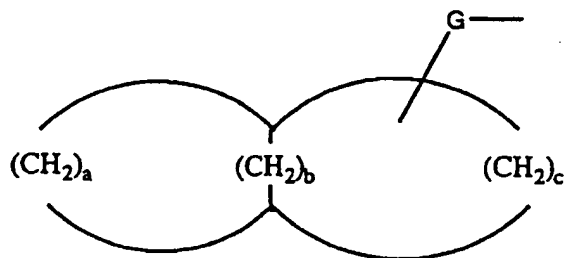


dans laquelle Ar représente

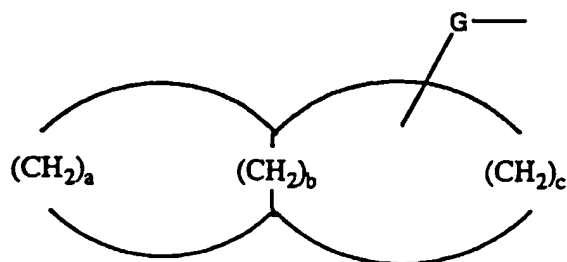




R_1 représente un groupe méthyle facultatif substitué sur un des trois atomes de carbone de connexion ;
 R_2 représente un atome d'hydrogène, un groupe alkyle en C_1 - C_4 , un groupe trifluorométhyle, un groupe hydroxyle, un groupe (alkyle en C_1 - C_4)-O-, un groupe (alkyle en C_1 - C_4)-S(O) $_p$ -, ou un atome d'halogène ;
 R_3 représente un groupe cycloalkyle en C_3 - C_8 ou un groupe bicycloalkyle répondant à la formule



où a et c valent, indépendamment l'un de l'autre, 1 - 5, b vaut 0 - 5, et (a + c) est supérieur à 2 ;
 Z représente un groupe alcane, alcène ou alcyne en C_4 - C_{10} linéaire ou ramifié ; un groupe (cycloalkyle en C_4 - C_8) facultativement substitué par un groupe alkyle en C_1 - C_4 ou par un groupe phényle ; un groupe bicycloalkyle répondant à la formule



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dans laquelle a et c valent, indépendamment l'un de l'autre, 1 - 5, b vaut 0 - 5, et (a + c) est supérieur à 2 ; un groupe alkyle en C₂-C₁₀ facultativement substitué par un groupe phényle, où le groupe phényle peut être facultativement substitué par R₂ tel qu'il a été défini précédemment; ou un groupe -(alkylidène en C₁-C₄)-T-(alkyle en C₁-C₄), où T représente un groupe -O-, un groupe -S-, un groupe -SO-, ou un groupe -SO₂;

où chaque G représente, indépendamment l'un de l'autre, une liaison ou un groupe alkylidène en C₁-C₄;

X représente un groupe -H, un groupe -COY, un groupe -CN, ou un groupe alkyle en C₁-C₄;

Y représente un groupe -OH, un groupe -O-(alkyle en C₁-C₄) ou un groupe -NH₂;

R_a et R_{a'} représentent, indépendamment l'un de l'autre, un atome d'hydrogène ou un groupe alkyle en C₁-C₃, ou lorsqu'ils sont pris ensemble avec l'atome de carbone auquel ils sont attachés, ils forment un noyau cycloalkyle en C₃-C₈;

p vaut 0, 1 ou 2 ;

A représente un groupe -O-, un groupe -S-, un groupe -NH- ou un groupe -NCH₃-; et

m vaut 0, 1, 2 ou 3 ;

et avec un troisième composant choisi dans le groupe constitué du L-tryptophane et du 5-hydroxy-L-tryptophane ;

ou un sel pharmaceutiquement acceptable de ceux-ci.

10. Composition selon la revendication 8, qui est adaptée à l'administration orale.

11. Composition selon la revendication 8, dans laquelle le composé servant de premier composant est la fluoxétine ou la duloxétine.

12. Composition selon la revendication 10, dans laquelle le composé servant de premier composant est la fluoxétine ou la duloxétine.

13. Composition selon la revendication 8, dans laquelle le composé servant de deuxième composant est le pindolol, le penbutolol, le propranolol, le tertatolol ou le 4-(2-hydroxy-3-cyclohexylaminopropoxy)indole.

14. Composition selon la revendication 12, dans laquelle le composé servant de deuxième composant est le pindolol, le penbutolol, le propranolol, le tertatolol ou le 4-(2-hydroxy-3-cyclohexylaminopropoxy)indole.